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GEOGRAPHICAL INDICATION



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Government Of India  
Patent Office  
Todi Estates, 3<sup>rd</sup> Floor,  
Lower Parel (West)  
Mumbai - 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy  
of Application and Complete Specification filed on 28/04/2004 in respect of Patent  
Application No.491/MUM/2004 of ALEMBIC LIMITED, ALEMBIC ROAD,  
VADODARA - 390 003, GUJARAT, INDIA, AN INDIAN COMPANY.

This certificate is issued under the powers vested in me under  
Section 147(1) of the Patents Act, 1970.

.....  
..... Dated this 16<sup>th</sup> day of May 2005.

( A. T. PATRE )  
ASSTT.CONTROLLER OF PATENTS & DESIGNS.

**FORM - 1**  
**THE PATENTS ACT, 1970**  
**(39 of 1970)**  
**APPLICATION FOR GRANT OF A PATENT**  
[See sections 5 (2), 7, 54 and 135 and rule 33A]

1. We, a) **ALEMBIC LIMITED**, b) Alembic Road, Vadodara-390 003, Gujarat, India, (c) An Indian Company,
2. hereby declare -
- (a) that we are in possession of an invention titled **"Process for the preparation of Telithromycin"**.
- (b) that the Complete specification relating to this invention is filed with this application.
- (c) that there is no lawful ground of objection to the grant of a patent to us.
3. further declare that the inventors for the said invention are
- a) SOHANI, Suhas, b) Alembic Limited, Alembic Road, Vadodara-390 003, Gujarat, India, c) an Indian national.
- a) DEODHAR, Mandar, b) Alembic Limited, Alembic Road, Vadodara-390 003, Gujarat, India, c) an Indian national.
- a) PATEL, Nishant, b) Alembic Limited, Alembic Road, Vadodara-390 003, Gujarat, India, c) an Indian national.
- a) PATEL, Manish, b) Alembic Limited, Alembic Road, Vadodara-390 003, Gujarat, India, c) an Indian national.
- a) DAVADRA, Mahesh b) Alembic Limited, Alembic Road, Vadodara-390 003, Gujarat, India, c) an Indian national.
- a) KANSAL, Vinodkumar, b) Alembic Limited, Alembic Road, Vadodara-390 003, Gujarat, India, c) an Indian national.
4. ~~We claim the priority from the application(s) filed in convention countries, particulars of which are as follows:-~~
5. ~~We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant/patentee:-~~
6. ~~We state that the application is divided out of our application, the particulars of which are given below and pray that this applica. on deemed to have been filed on \_\_\_\_\_ under section 16 of the Act~~
7. That we are the assignees of the true and first inventors.

DUPLICATE

491 | मुंबई | 2004  
MUM  
28 APR 2004

8. That our address for service in India is as follows :

S. MAJUMDAR & CO., 5, Harish Mukherjee Road, Calcutta - 700 025, State of West Bengal. Phone : 0-33-24557484/24557485/24557486 ; Fax : 0-33-24557487/24557488.  
E-mail: [cal@patentindia.com](mailto:cal@patentindia.com)

9. We are the true and first inventors for this invention declare that the applicant(s) herein are our assignee

- a) SOHANI, Suhas
- b) Alembic Limited, Alembic Road, Vadodara-390 003, Gujarat, India
- c) An Indian national.

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SOHANI, Suhas

- a) DEODHAR, Mandar
- b) Alembic Limited, Alembic Road, Vadodara-390 003, Gujarat, India
- c) An Indian national.

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DEODHAR, Mandar

- a) PATEL, Nishant
- b) Alembic Limited, Alembic Road, Vadodara-390 003, Gujarat, India
- c) An Indian national.

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PATEL, Nishant

- a) PATEL, Manish
- b) Alembic Limited, Alembic Road, Vadodara-390 003, Gujarat, India
- c) An Indian national.

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PATEL, Manish

- a) DAVADRA, Mahesh
- b) Alembic Limited, Alembic Road, Vadodara-390 003, Gujarat, India
- c) An Indian national.

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DAVADRA, Mahesh

- a) KANSAL, Vinodkumar
- b) Alembic Limited, Alembic Road, Vadodara-390 003, Gujarat, India
- c) An Indian national.

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KANSAL, Vinodkumar

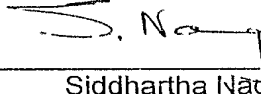
10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:

- a) Complete specification (3 copies).
- b) Statement and Undertaking on FORM -3 (in duplicate).
- c) Fee of Rs. 3000/- by Cheque No. 620766 dated 23-04-04 drawn on Standard Chartered Bank.

We request that a patent may be granted to us for the said invention.

Dated this 23<sup>rd</sup> day of April 2004



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Siddhartha Nag  
Of S. Majumdar & Co.  
Applicant's Agent

To  
The Controller of Patents  
The Patent Office  
At Mumbai

FORM - 2

THE PATENTS ACT, 1970

( 39 OF 1970 )

COMPLETE SPECIFICATION

( See Section 10 )

1. TITLE OF INVENTION

PROCESS FOR THE PREPARATION OF TELITHROMYCIN

DUPLICATE

2. **ALEMBIC LIMITED**, Alembic Road, Vadodara-390 003, Gujarat, India, an Indian Company.

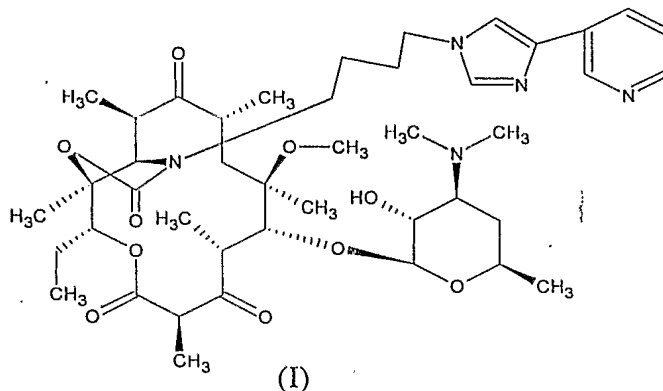
The following specification particularly describes the nature of the invention and the manner in which it is to be performed.

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## Field of the invention

The present invention relates to the process for the preparation of Telithromycin of Formula (I) and its pharmaceutically acceptable salts.



Telithromycin of formula (I) has an antibiotic activity.

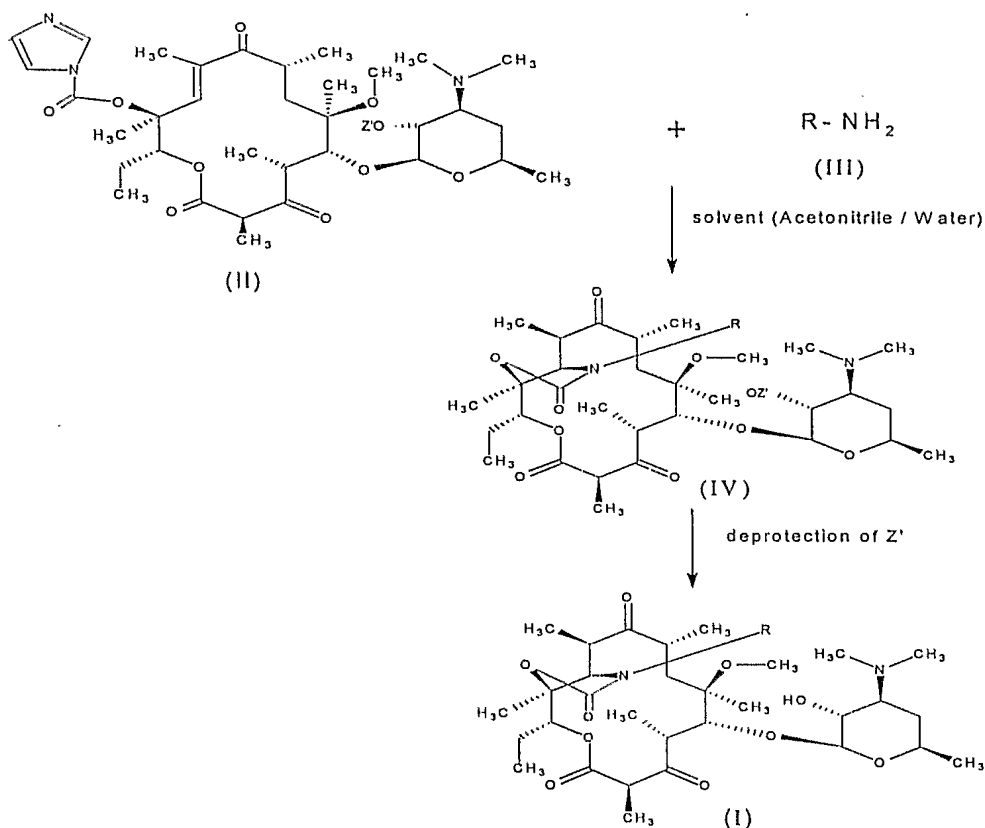
## Background of the invention

Macrolide compounds are known for anti bacterial activity. The rapid development of antibiotic resistance among the major respiratory pathogens has created a serious problem for the effective management of respiratory tract infections. There is a great medical need for new antibiotics to address the problem of antibiotic resistance. Under these circumstances, several novel series of macrolides with a common C-3 ketone group were recently introduced, which are collectively known as ketolides.

Ketolides represent a novel class of macrolide antibiotics that have received much attention recently on account of their excellent activity against resistant organisms. Most ketolides are derivatives of erythromycin, a potent and safe antibiotic widely prescribed for the treatment of respiratory tract infections for more than four decades. Ketolides are 14-membered ring macrolide derivatives characterized by a keto group at the C-3 position [Curr. Med. Chem. – Anti-Infective Agents, 2002, 1, 15-34]. Several Ketolide compounds are under clinical investigation. However, Telithromycin of Formula (I) is the first agent to receive approvable status in this class of drugs.

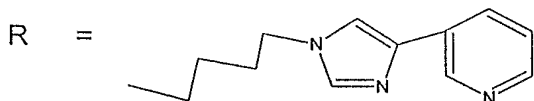
US patent 5635485 discloses several ketolide compounds, which are prepared by condensing compounds of Formula (II) with amine of formula (III) in a solvent for prolonged hours to yield compound of formula (IV), followed by removal of protecting group Z' at 2' position by hydrolysis as shown in Scheme -1. Furthermore, Formula (II) has been prepared by following US 5527780.

SCHEME - 1



wherein, definition of R and Z' as defined in above referred patent.

Accordingly, Telithromycin is prepared by condensing compound of formula (II) with amine of formula (III), where in



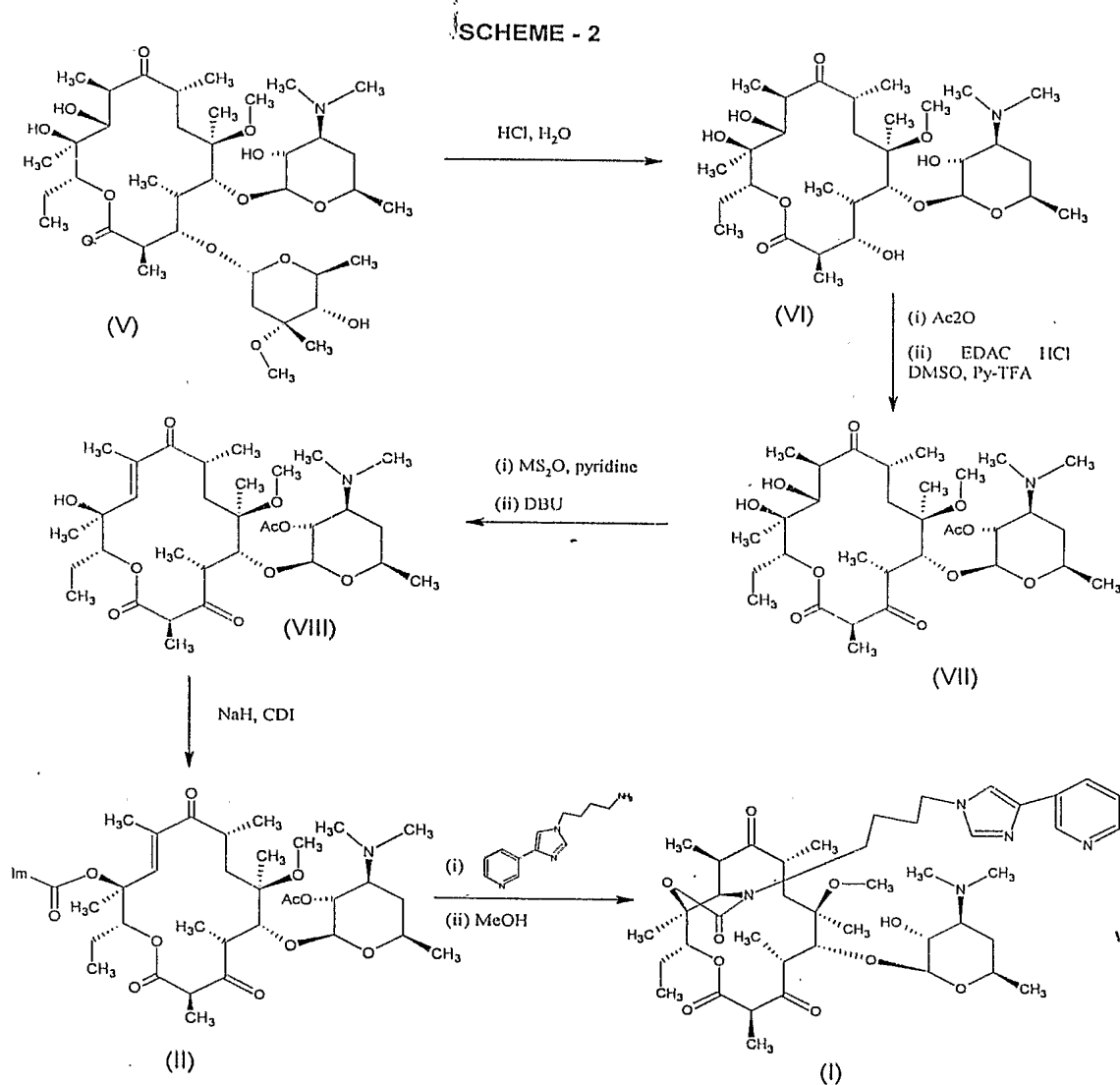
followed by removing the protecting group to yield telithromycin of formula (I). The preparation of formula II is disclosed in Current Medicinal chemistry, 2001, Vol. 8, 1727-1758. The process described in US 5635485 suffers several drawbacks such as

- (i) Condensation of formula II with formula III is cumbersome and it is very difficult to remove unreacted reagents and impurities formed during the reaction.
- (ii) The isolation and purification of the desired compound of Formula (I) cannot be done without laborious column chromatography, which is not viable at commercial production level.

Current Medicinal Chemistry, 2001, Vol. 8, 1727-1758 also describes the process for the preparation of various ketolides, including Telithromycin in which Clarithromycin (formula V) is reacted with hydrochloric acid to remove cladinose ring at C-3 position (formula VI)



followed by selective acetylation of the 2'-hydroxy group in formula VI and selective oxidation of the 3-hydroxy group generated ketolide of formula VII. Further, 11-hydroxy group of compound of formula (VII) is selectively mesylated followed by base induced  $\beta$ -elimination to furnish  $\alpha,\beta$ -unsaturated ketone (formula VIII). The compound of formula (VIII) is further treated with sodium hydride and carbonyldiimidazole to form 12-O-acyl imidazole of formula (II), which upon stereoselective cyclization with (4-(3-pyridinyl)-imidazol-1-yl)-butylamine and subsequent deprotection of the 2'-hydroxy group gives Telithromycin of Formula (I). This process is outlined in following SCHEME - 2



However, this process consists of several difficulties as explained in earlier prior art process and moreover other difficulties such as use of pyrophoric material like  $\text{NaH}$ , which is hazardous and extremely difficult to handle at the plant scale.

In light of the above difficulties for the preparation of Telithromycin, this process is not suitable for commercial production level.

### Objects of the invention

Therefore the basic object of this invention is to provide a process for the preparation of Telithromycin, which would overcome the drawbacks, and shortcomings of the prior arts.

Another object of the present invention is to provide a process for the preparation of Telithromycin, which would be high yielding, cost effective, easy to operate at industrial scale and would not involve the use of moisture sensitive, pyrophoric compounds such as sodium hydride.

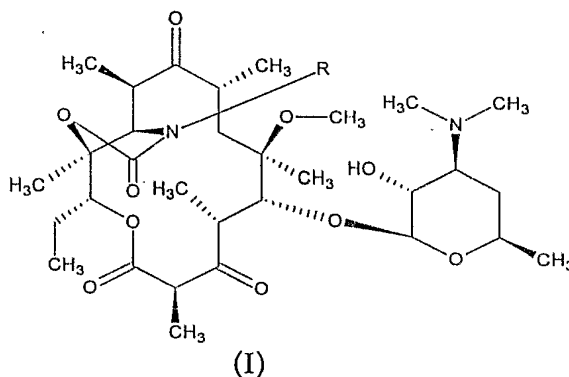
Another object of the present invention is to provide a process of manufacture of Telithromycin, which lead to the removal of reagents and side products by intermediate crystallization. Thus isolation of final product enabling good yield and purity, without column chromatography.

A further objective of the invention is to provide a process of manufacture of Telithromycin that would involve selective mild reaction conditions.

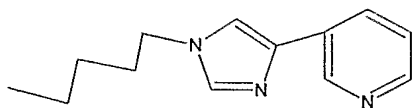
A further object of the invention is to provide a process of manufacture of Telithromycin that would be industrially feasible.

### Summary of the invention:

The present invention provides the process for the preparation of Telithromycin (Formula I) or its pharmaceutically acceptable salts

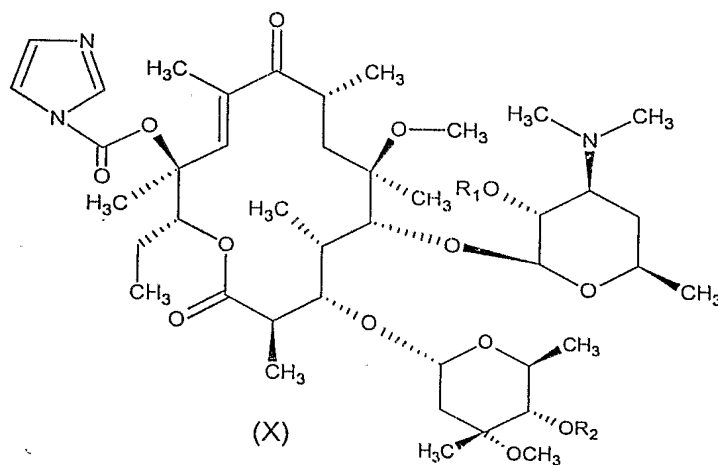
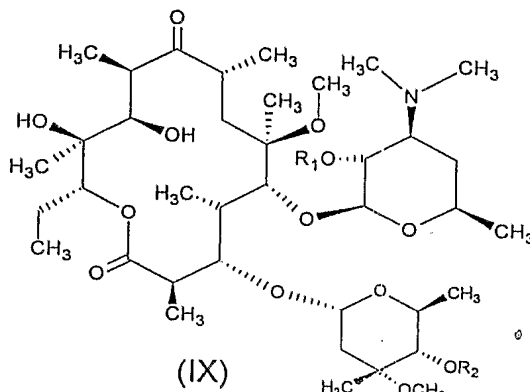


where, R is

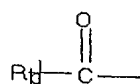


comprising

- a) reacting compound of formula (IX) with carbonyldiimidazole in presence of polar solvent and base to obtain 10,11-Anhydro-2'4"-di-O-acetyl-12-O-imidazolyl carbonyl-6-O-methylerythromycin A of formula (X).



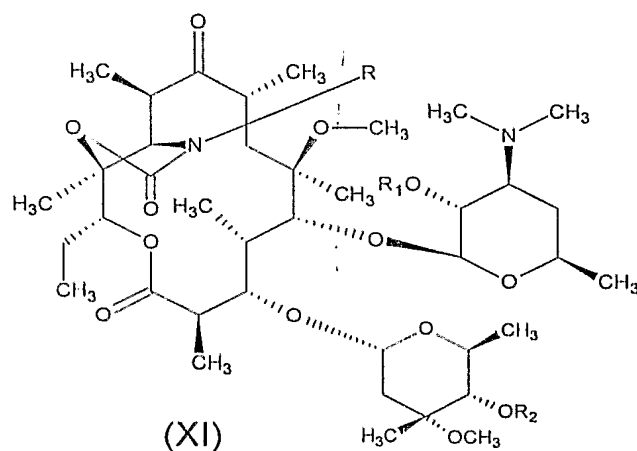
where  $R_1$  and  $R_2$  are same or different protecting groups selected from,



$R_b$  is C1 to C10 alkyl group or aryl group, preferably C1 – C4 alkyl group,

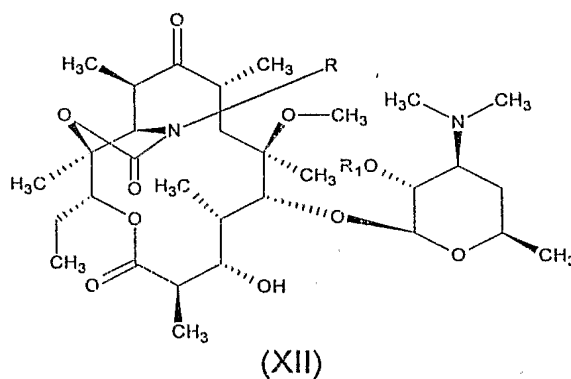
$R_1$  and  $R_2$  are also same or different acetyl or benzyl group,

- b) condensing the compound of formula (X) with  $R-NH_2$  in suitable polar solvent to give compounds of formula (XI).

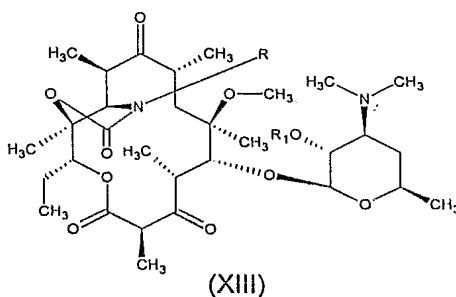


where R is as defined above and R<sub>1</sub> and R<sub>2</sub> are also same as defined above.

c) treating the compound of formula (XI) with acid to obtain compound of formula (XII)



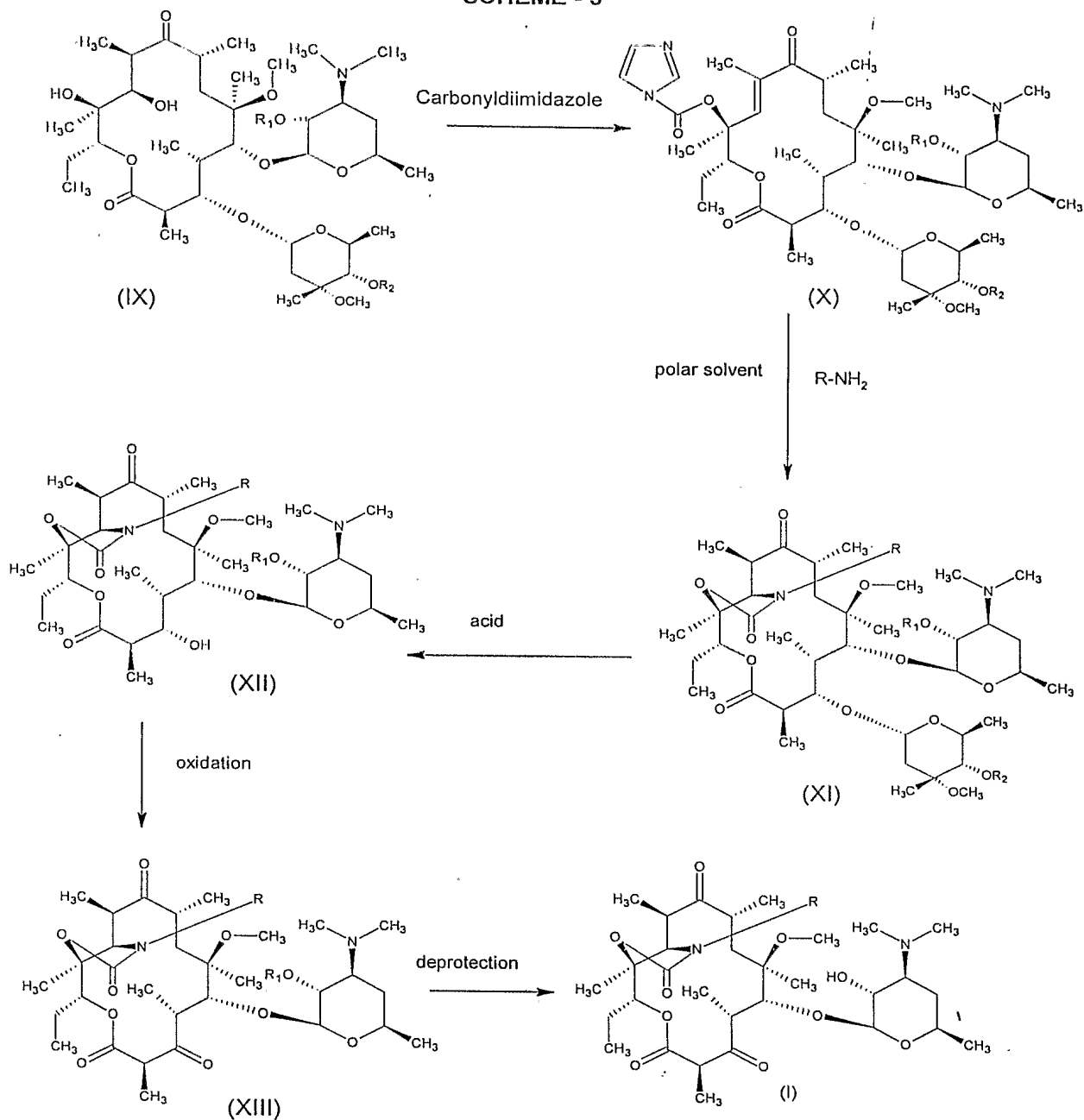
d) oxidising the resulting compound of formula (XII) in presence of suitable oxidizing agent at C-3 position to give compounds of formula (XIII)



(e) removing the protecting group of formula (XIII) by treating with alcohol to give desired compounds of Formula (I)

The reaction scheme followed is as shown in Scheme-3 hereunder:

SCHEME - 3



The polar solvent use in step (a) is selected from dimehtylformamide, tetrahydrofuran, acetonitrile and mixtures thereof.

The base used in step (a) is selected from DBU, Triethylamine, diisopropylethylamine.

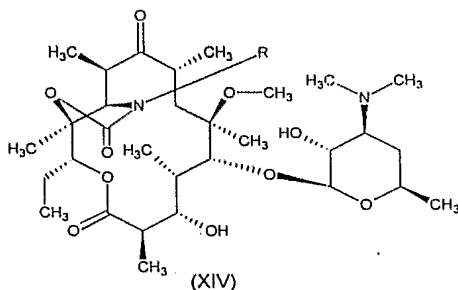
The polar solvent used in step (b) is a polar aprotic solvent or polar protic solvent. The solvent is selected from the group comprises of methanol, ethanol, propanol, butanol, i-butyl alcohol, t-butyl alcohol, methoxyethanol, ethoxyethanol, pentanol, neo-pentyl alcohol, t-

pentyl alcohol, cyclohexanol, ethylene glycol, propylene glycol, benzyl alcohol, phenol, glycerol, dimethylformamide (DMF), dimethylacetamide (DMAC), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMI), N-methylpyrrolidinone (NMP), formamide, N-methylacetamide, N-methylformamide, acetonitrile, dimethylsulfoxide, propionitrile, ethyl formate, methyl acetate, hexachloroacetone, HMPA, HMPT, acetone, ethyl methyl ketone, ethyl acetate, isopropyl acetate, t-butyl acetate, sulfolane, N,N-dimethylpropionamide, nitromethane, nitrobenzene, tetrahydrofuran (THF), dioxane, polyethers or water or mixtures thereof.

The oxidation in step (d) is carried out by using the commonly used oxidising reagents such as Corey- Kim oxidation method, Des- Martins reagent, Pfitzner moffat method or modifications thereof or with dimethyl sulfoxide in presence of oxalyl chloride or phosphorous pentoxide or p-Toluene sulfonyl chloride or acetic anhydride. The oxidation can also be carried out by Manganese or chromium or selenium reagents, tert-amine oxides or by any above oxidant in presence of phase transfer catalyst.

Alternatively, compounds of formula (XII) as obtained in step (c) is converted to compounds of formula (I) by the steps of :

(d) treating compounds of formula (XII) as received from step (c) with alcohol to give compounds of formula (XIV)



(e) selective oxidization of resulting compounds of formula (XIV) of step (f) in the presence of oxidizing agent to form desired ketolide compound of formula (I)

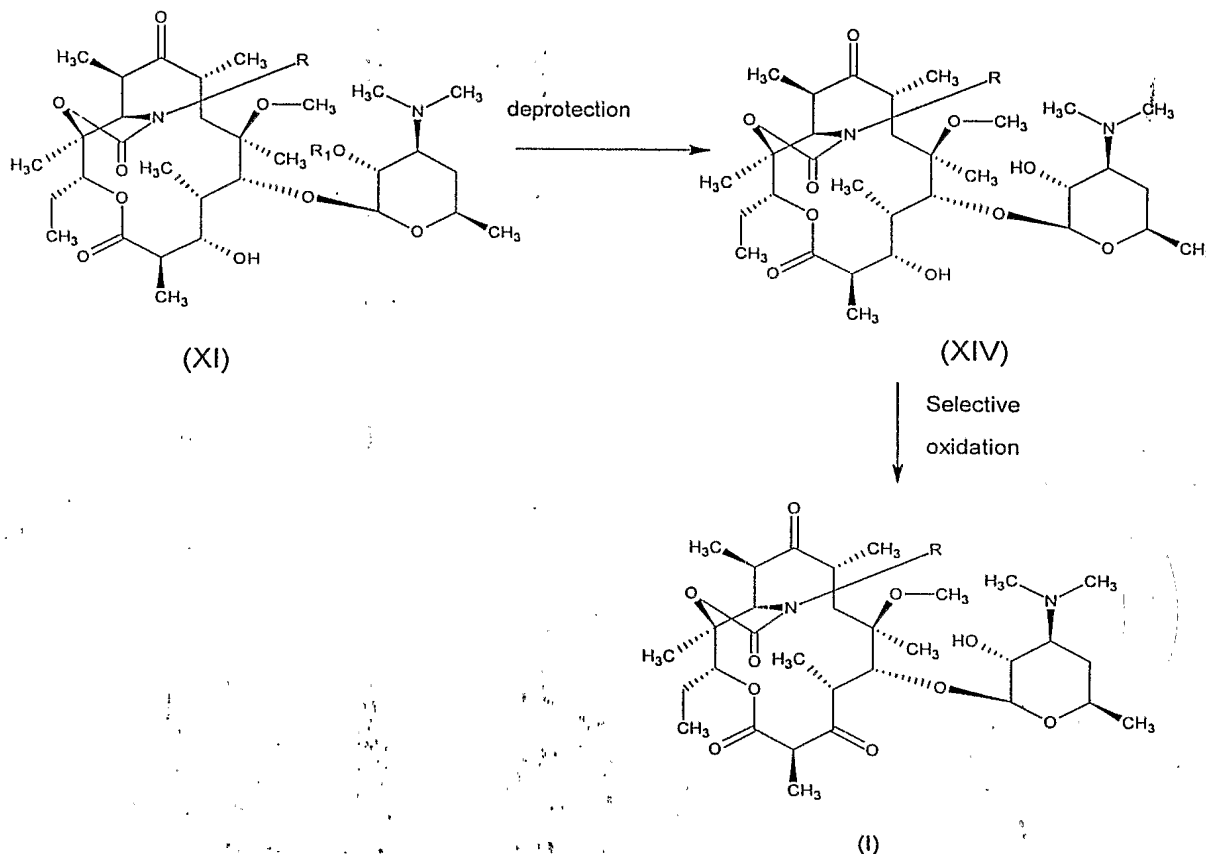
Optionally the compound of formula XIV may be crystallized using a polar solvent selected from acetone, alcohol, ethyl acetate, preferably acetone.

The oxidation can be carried out by using suitable oxidising system reported in the literature such as Corey- Kim oxidation method, Des- Martins reagent, Pfitzner moffat method or modifications thereof or with dimethyl sulfoxide in presence of oxalyl chloride or phosphorous pentoxide or p-Toluene sulfonyl chloride or acetic anhydride. The oxidation can also be carried out by manganese or chromium or

selenium reagents, tert-amine oxides or any above oxidant in presence of by phase transfer catalyst.

The reaction scheme followed is as shown in Scheme-4 hereunder:

SCHEME - 4



#### Detailed description of the invention

The present invention relates to the process for the preparation of Telithromycin of formula (I) comprising:

- (i) reacting 2'4"-di-O-acetyl-6-O-methylerythromycin A (obtained as indicated in example 1(1) of U.S. patent US 5591837) with carbonyldiimidazole in presence of polar solvent and base to give 10,11-Anhydro-2'4"-di-O-acetyl-12-O-imidazolyl carbonyl-6-O-methylerythromycin A, the polar solvent being selected from Dimethylformamide, Tetrahydrofuran, Acetonitrile and mixtures thereof and the base selected from DBU, Triethylamine, diisopropylethylamine.

- (ii) condensing 10,11-anhydro-2'4"-di-O-acetyl-12-O-imidazolyl carbonyl-6-O-methylerythromycin A with 4-[4-(3-pyridyl)imidazol-1-yl]butaneamine in a polar solvent at 5° to 120°C to give 2',4"-di-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-11-deoxy-6-O-methylerythromycin A 11,12-cyclic carbamate, said polar solvent is polar aprotic solvent or polar protic solvent;
- (iii) reacting 2',4"-di-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-11-deoxy-6-O-methylerythromycin A 11,12-cyclic carbamate with acid at 0°C to 100° C by removal cladinose ring at C-3 position to obtain 2'-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-11-deoxy-5-O-desosaminy-6-O-methylerythronolide A 11,12-cyclic carbamate.
- (iv) Further, 2'-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-11-deoxy-5-O-desosaminy-6-O-methylerythronolide A 11,12-cyclic carbamate is oxidized at C-3 position to give 2'-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-11-deoxy-3-oxo-5-O-desosaminy-6-O-methylerythronolide A 11,12-cyclic carbamate;
- (v) 2'-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-11-deoxy-3-oxo-5-O-desosaminy-6-O-methylerythronolide A 11,12-cyclic carbamate is further treated with alcohols to remove protecting group at 2' position to give Telithromycin of formula (I).

In step (ii) of the process the polar solvents is selected from the group comprises of methanol, ethanol, propanol, butanol, i-butyl alcohol, t-butyl alcohol, methoxyethanol, ethoxyethanol, pentanol, neo-pentyl alcohol, t-pentyl alcohol, cyclohexanol, ethylene glycol, propylene glycol, benzyl alcohol, phenol, glycerol, dimethylformamide (DMF), dimethylacetamide (DMAC), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMI), N-methylpyrrolidinone (NMP), formamide, N-methylacetamide, N-methylformamide, acetonitrile, dimethylsulfoxide, propionitrile, ethyl formate, methyl acetate, hexachloroacetone, HMPA, HMPT, acetone, ethyl methyl ketone, ethyl acetate, isopropyl acetate, t-butyl acetate, sulfolane, N,N-dimethylpropionamide, nitromethane, nitrobenzene, tetrahydrofuran (THF), dioxane, polyethers or water or mixtures thereof.



The preferred polar solvent is dimethylformamide (DMF) and acetonitrile.

The most preferred solvent is dimethylformamide.

The reaction step is carried out at 5 to 120° C. Preferably step (i) can be carried out at 30 to 60° C. The reaction also can be carried out in water or the mixture of water and organic solvents (as mentioned above).

The ratio of substrate to amine is 1: 3 mole and the preferably ratio is 1:2 mole.

In step (iii) of the process the acid is selected from organic acid or inorganic acid or mixtures thereof. Inorganic acid can be mineral acid selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and perchloric acid, hydrofluoric acid. The acid is preferably hydrochloric acid.

The solvent is selected from the group comprising water or polar organic solvents like alcohols or mixtures thereof. The preferred solvents can be water, methanol, ethanol, iso propanol, n- butanol, tert-butanol or mixtures thereof.

The reaction step is carried out at 0 to 70° C and more preferably 20°C to 60°C for 6 to 48 hrs.

In step (iv) of the process the oxidation can be carried out by way of Corey- Kim oxidation method, Des- Martins reagent, Pfitzner moffat method or modifications thereof or with dimethyl sulfoxide in presence of oxalyl chloride or phosphorous pentoxide or p-Toluene sulfonyl chloride or acetic anhydride. The oxidation can also be carried out by Manganese or chromium or selenium reagents, tert-amine oxides or any above oxidant in presence of phase transfer catalyst.

In step (v) of the process the alcohol is selected from the group comprising of methanol, ethanol, n-propanol, isopropanol, n-butanol, tert-butanol or mixtures there of or with water at 0°C to 100°C to give desired ketolide compounds of formula (I).

Alternatively, pure and commercially viable process for the preparation of Telithromycin is by using first deprotection of 2'-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl) imidazol-1-yl] butyl]-11-deoxy-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate as obtained in step (iii) purification and then oxidation of the resultant compound.

The detail process is described as below:

(vi) 2'-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl) imidazol-1-yl] butyl]-11-deoxy-5-O-desosaminy-6-O-methylerythronolide A 11,12-cyclic carbamate is treated with an alcohol at 0 to 70°C or with water at 0° to 100° to remove acetyl protecting group and form 2'-hydroxy -11-amino-11-N-[4-[4-( 3-pyridyl) imidazol-1-yl] butyl]-11-deoxy-5-O-desosaminy-6-O-methylerythronolide A 11,12-cyclic carbamate or with water at 0°C to 100°C to give desired compound of formula (XIV) the compound of formula (XIV) is crystallised by using polar solvent;

(vii) 2'-hydroxy -11-amino-11-N-[4-[4-( 3-pyridyl ) imidazol-1-yl] butyl]-11-deoxy-5-O-desosaminy-6-O-methylerythronolide A 11,12-cyclic carbamate is selectively oxidized at C-3 position to form Telithromycin of formula (I).

In step (vi) the alcohol is selected from the group comprising of methanol, ethanol, n-propanol, isopropanol, n-butanol, tert-butanol or mixtures thereof. In the said step the polar solvent is selected from acetone or alcohol or ethyl acetate or mixture thereof. The solvent used for the crystallisation of formula (XIV) is preferably acetone.

In step (vii) the oxidation is carried out by way of Corey- Kim oxidation method, Des- Martins reagent , Pfitzner moffat method or modifications thereof or with dimethyl sulfoxide in presence of oxalyl chloride or phosphorous pentoxide or p-Toluene sulfonyl chloride or acetic anhydride. The oxidation can also be carried out by manganese or chromium or selenium reagents, tert-amine oxides or any above oxidant in presence of phase transfer catalyst.

The process of the present invention is described by the following examples, which are illustrative only and should not be construed so as to limit the scope of the invention in any manner.

#### **EXAMPLES:**

**Example 1:** Preparation of 10,11-Anhydro-2'4"-di-O-acetyl-12-O-imidazolyl carbonyl-6-O-methylerythromycin A.

Mix 10 gm of 2',4"-di-O-acetyl-6-O-methylerythromycin A, 10 gm of carbonyldiimidazole, 40 ml dimethylformamide and 4 ml DBU at room temperature. The solution was cleared. The clear solution was stirred for 3 hrs. The reaction mixture was quenched with water (400ml). The solid was filtered and washed with water. The wet solid was dissolved in dichloromethane and the organic layer was separated. The solvent was removed under vacuum. Add diisopropylether (40 ml) and the reaction mixture was stirred for half an hour. The solid was filtered and washed with diisopropylether (2 X 5 ml). The solid was dried at

room temperature to give 9.0 gm of 10,11-Anhydro-2'4"-di-O-acetyl-12-O-imidazolylcarbonyl-6-O- methyl erythromycin A.

**Example 2:** Preparation of 2',4"-di-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-11-deoxy-6-O-methylerythromycin A 11,12-cyclic carbamate.

20gm of 10,11-Anhydro-2'4"-di-O-acetyl-12-O-imidazolylcarbonyl-6-O- methyl erythromycin A was added in 9.6 gm of 4-[4-(3-pyridyl) imidazol-1-yl] butanamine and 100ml Dimethyl formamide and stirred at 50 °C for 18 hours. The reaction mixture was then diluted with water and stirred for 30min. The precipitated solid was filtered and washed with water. Further, it was dried at 50 °C under vacuum to give 18gm of 2', 4"-di-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-11-deoxy-6-O-methylerythromycin A 11,12-cyclic carbamate.

**Example 3:** Preparation of 2'-O-acetyl-11-amino-11-N-[4-[4-( 3-pyridyl ) imidazol-1-yl] butyl]-11-deoxy-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate.

23g of 2',4"-di-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-11-deoxy-6-O-methylerythromycin A 11,12-cyclic carbamate was dissolved in solution of 23ml concentrated hydrochloric acid and 230ml water. The mixture was stirred at ambient temperature for 12 hours. The reaction mixture was then basified with sodium hydroxide when a white solid was obtained. The solid was filtered and washed with water. Drying at ambient temperature afforded 16gm of 2'-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl) imidazol-1-yl] butyl]-11-deoxy-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate. The product can be used in the next step without further purification.

**Example 4:** Preparation of 2'-O-acetyl-11-amino-11-N-[4-[4-( 3-pyridyl ) imidazol-1-yl] butyl]-11-deoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

15g of 2'-O-acetyl-11-amino-11-N-[4-[4-( 3-pyridyl ) imidazol-1-yl] butyl]-11-deoxy-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate was dissolved in 150 ml dichloromethane and 22.5g of Des Martin's reagent was added in one lot. The mixture was stirred at ambient temperature for 1 hour. Further, added the mixture of 260 ml saturated sodium bicarbonate solution and saturated sodium thiosulfate solution and stirred the mixture for 20 min. Filtered off the formed solid precipitate and separated the organic layer. Washed the organic layer with water, dried over sodium sulfate and distilled off the solvent under vacuum to give 13gm of 2'-O-acetyl-11-amino-11-N-[4-[4-( 3-pyridyl ) imidazol-1-yl] butyl]-11-deoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate.

**Example 5:** Preparation of 2'-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-11-deoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

10g of 2'-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-11-deoxy-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate was dissolved in 100 ml dichloromethane. Dimethyl sulfoxide (16.6 ml), Cyclohexyl dimethyl amino propyl carbodimide Hydro chloride (25.0g) and Pyridine HCl (12.1 gm) was added in one lot. The mixture was stirred at ambient temperature (20-30°C) for 6 hour. Further, 500 ml water was added and stirred the mixture for 30 min. The organic layer was separated and washed with water, dried over sodium sulfate and distilled off the solvent under vacuum to give 7.05 gm of 2'-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-11-deoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate.

**Example 6:** Preparation of 2'-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-11-deoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate

N-Chloro succinimide (4.68 gm) was charged to the reaction vessel under nitrogen atmosphere and Dichloromethane (200 ml) was added slowly. The reaction masses was cooled to 0°C, Dimethyl sulfide (3.5 ml) was added slowly and continue the stirring at same temperature for half an hour. The reaction mass was cooled to -25°C and 2'-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-11-deoxy-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate (10g) dissolved in 50 ml dichloromethane was added slowly. The mixture was stirred at -25°C temperature for 2 hour. At the same temperature Diisopropylethyl amine (0.6ml) was added and the reaction mixture was stirred for an hour. Water (500 ml) was added and stirred the mixture for 30 min. The organic layer was separated and washed with water, dried over sodium sulfate and distilled off the solvent under vacuum to give 7.5 gm of 2'-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-11-deoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate.

**Example 7:** 11-Amino-11-N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-11-deoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate [Telithromycin] (II)

A solution for 10g of 2'-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-11-deoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate in 100ml methanol was stirred at ambient temperature for 16 hours. Further, solvent was distilled off under vacuum and stirring remain solid with 50ml diisopropyl ether to gave 7gm of desired compound 11-Amino-11-N-[4-[4-(3-pyridyl)imidazol-1-yl]butyl]-11-deoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate [Telithromycin] (I).

**Example 8:** 11-Amino-11-N-[4-[4-(3-pyridyl) imidazol-1-yl]butyl]-11-deoxy-3-oxo-5-O-desosaminy-6-O-methylerythronolide A 11,12-cyclic carbamate [Telithromycin] (II)

A solution for 10g of 2'-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl) imidazol-1-yl] butyl]-11-deoxy-3-oxo-5-O-desosaminy-6-O-methylerythronolide A 11,12-cyclic carbamate in 100ml *Isopropanol* was stirred at ambient temperature for 24 hours. Further, solvent was distilled off under vacuum and equilibrating remain solid with 50ml diisoproyl ether to gave 7gm of desired compound 11-Amino-11-N-[4-[4-(3-pyridyl) imidazol-1-yl]butyl]-11-deoxy-3-oxo-5-O-desosaminy-6-O-methylerythronolide A 11,12-cyclic carbamate [Telithromycin] (I).

**Example 9:** 2'-hydroxy -11-amino-11-N-[4-[4-(3-pyridyl) imidazol-1-yl] butyl]-11-deoxy-5-O-desosaminy-6-O-methylerythronolide A 11,12-cyclic carbamate.

10g of 2'-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl) imidazol-1-yl] butyl]-11-deoxy-5-O-desosaminy-6-O-methylerythronolide A 11,12-cyclic carbamate in 100 ml methanol was stirred at reflux temperature for 6 hours. The solvent was then distilled off under vacuum to give crude product as white foam. Then, the crude product was purified by refluxing in 20 ml of acetone followed by 1 hour stirring at 10°C. Filtered off the solution and washed the solid and with 2x5 ml of chilled acetone to gave 8.0gm 2'-hydroxy -11-amino-11-N-[4-[4-(3-pyridyl) imidazol-1-yl] butyl]-11-deoxy-5-O-desosaminy-6-O-methylerythronolide A 11,12-cyclic carbamate

**Example 10:** 2'-hydroxy -11-amino-11-N-[4-[4-(3-pyridyl) imidazol-1-yl] butyl]-11-deoxy-5-O-desosaminy-6-O-methylerythronolide A 11,12-cyclic carbamate.

10g of 2'-O-acetyl-11-amino-11-N-[4-[4-(3-pyridyl) imidazol-1-yl] butyl]-11-deoxy-5-O-desosaminy-6-O-methylerythronolide A 11,12-cyclic carbamate in 100 ml *Isopropanol* was stirred at reflux temperature for 18 hours. The solvent was then distilled off under vacuum to give crude product as white foam. Then, the crude product was purified by refluxing in 20 ml of acetone followed by 1 hour stirring at 10°C. Filtered off the solution and washed the solid and with 2x5 ml of chilled acetone to gave 8.0gm 2'-hydroxy -11-amino-11-N-[4-[4-(3-pyridyl) imidazol-1-yl] butyl]-11-deoxy-5-O-desosaminy-6-O-methylerythronolide A 11,12-cyclic carbamate

**Example 11:** 11-Amino-11-N-[4-[4-(3-pyridyl) imidazol-1-yl]butyl]-11-deoxy-3-oxo-5-O-desosaminy-6-O-methylerythronolide A 11,12-cyclic carbamate [Telithromycin] (Formula I)

10g of 2'-hydroxy -11-amino-11-N-[4-[4-(3-pyridyl) imidazol-1-yl] butyl]-11-deoxy-5-O-desosaminy-6-O-methylerythronolide A 11,12-cyclic carbamate was dissolved in 200 ml dichloromethane and 15g of Des Martin's reagent was added in one lot. The mixture was

stirred at ambient temperature for 30 min. Further, 260 ml of saturated sodium bicarbonate solution added and stirred the mixture for 30 min. Filtered off the solid precipitate and separated the organic layer. Washed the organic layer with water, dried over sodium sulfate and distilled off the solvent under vacuum to give solids. Further, it was stirred with 40ml of diisopropyl ether and filtered off and dried to give 9gm 11-Amino-11-N-[4-[4-(3-pyridyl) imidazol-1-yl]butyl]-11-deoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate [Telithromycin](I).

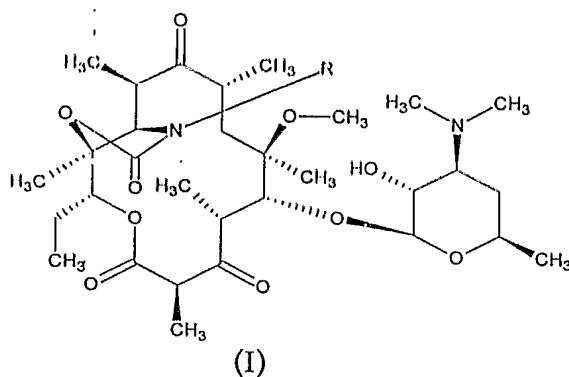
**Example 12:** 11-Amino-11-N-[4-[4-(3-pyridyl) imidazol-1-yl]butyl]-11-deoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate [Telithromycin] (Formula I)  
10g of 2'-hydroxy -11-amino-11-N-[4-[4-( 3-pyridyl ) imidazol-1-yl] butyl]-11-deoxy-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate was dissolved in 100 ml dichloromethane. Dimethyl sulfoxide (16.6 ml), Cyclohexyl dimethyl amino propyl carbodimide Hydro chloride (25.0g) and Pyridine HCl (12.1 gm) was added in one lot. The mixture was stirred at ambient temperature (20-30°C) for 6 hour. Further, 500 ml water was added and stirred the mixture for 30 min. The organic layer was separated and washed with water, dried over sodium sulfate and distilled off the solvent under vacuum to give 8.05 gm of 11-Amino-11-N-[4-[4-(3-pyridyl) imidazol-1-yl]butyl]-11-deoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate [Telithromycin](I).

**Example 13:** 11-Amino-11-N-[4-[4-(3-pyridyl) imidazol-1-yl]butyl]-11-deoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate [Telithromycin] (Formula I)

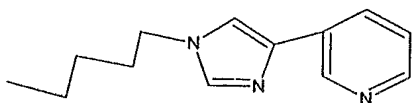
N-Chloro succinimide (4.68 gm) was charged to the reaction vessel under nitrogen atmosphere and Dichloromethane (200 ml) was added slowly. The reaction masses was cooled to 0°C, Dimethyl sulfide (3.5 ml) was added slowly and continue the stirring at same temperature for half an hour. The reaction mass was cooled to -25°C and 2'-hydroxy -11-amino-11-N-[4-[4-( 3-pyridyl ) imidazol-1-yl] butyl]-11-deoxy-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate (10g) dissolved in 50 ml dichloromethane was added slowly. The mixture was stirred at -25°C temperature for 2 hour. At the same temperature Diisopropylethyl amine (0.6ml) was added and the reaction mixture was stirred for half an hour. Water (500 ml) was added and stirred the mixture for 30 min. The organic layer was separated and washed with water, dried over sodium sulfate and distilled off the solvent under vacuum to give 6.5 gm of 11-Amino-11-N-[4-[4-(3-pyridyl) imidazol-1-yl]butyl]-11-deoxy-3-oxo-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbamate [Telithromycin] (Formula I).

**We Claim:**

1. A process for the preparation of compounds of formula (I) or its pharmaceutically acceptable salts

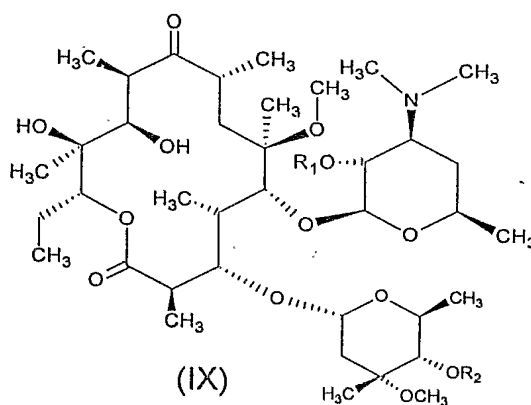


where, R is

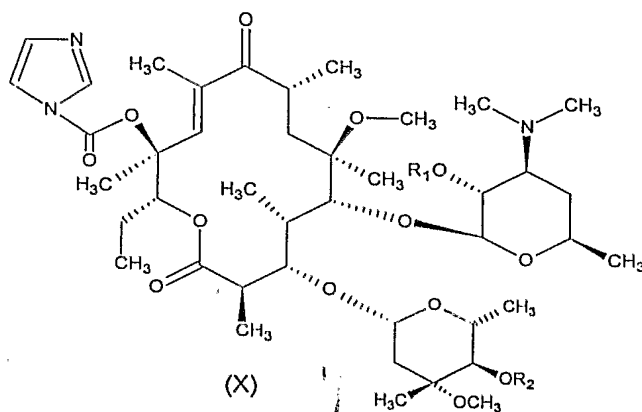


the process comprising the steps of

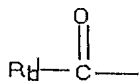
- (a) reacting compound of formula (IX) with carbonyldiimidazole in presence of a polar solvent and base to obtain



10,11-Anhydro-2'4"-di-O-acetyl-12-O-imidazolyl carbonyl-6-O-methylerythromycin A of formula (X),



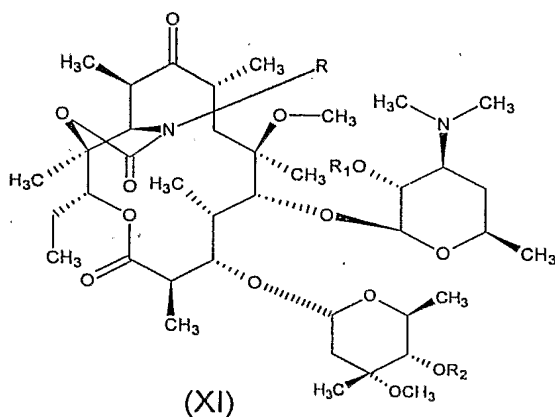
where  $R_1$  and  $R_2$  are same or different protecting groups selected from,



$R_b$  is C1 to C10 alkyl group or aryl group, preferably C1 to C4 alkyl group,

$R_1$  and  $R_2$  are also same or different acetyl group or benzyl group;

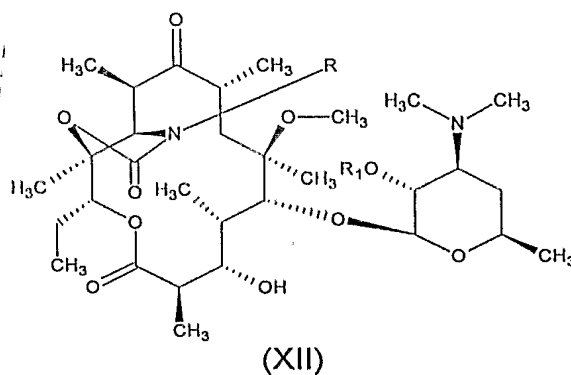
- (b) condensing the compounds of formula (X) with  $R-NH_2$  in a suitable polar solvent to obtain compounds of formula (XI)



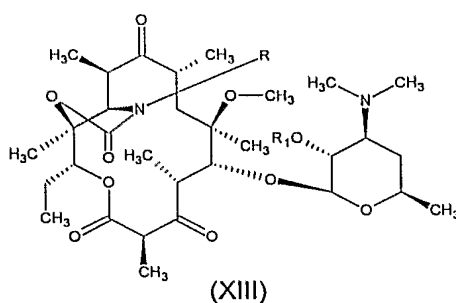
where  $R$  is as defined above and  $R_1$  and  $R_2$  are same or different protecting groups as described above;

- (c) treating the obtained compound formula (XI) with an acid to give compound of formula (XII)



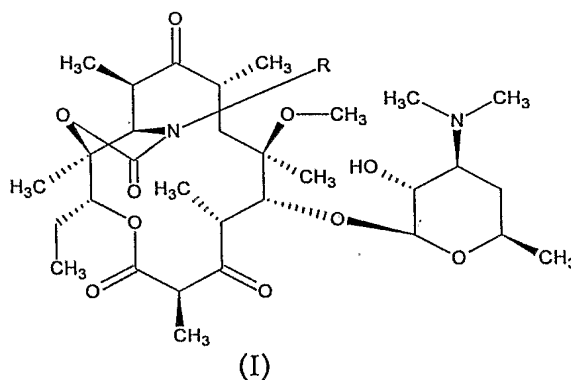


(d) oxidizing the resulting compounds of formula (XII) in presence of oxidizing agent to form compounds of formula (XIII)

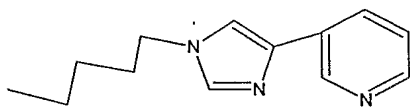


(e) removing the protecting group of formula (XIII) by treating with an alcohol to give desired compounds of Formula (I)

2. A process for the preparation of compounds of formula (I) or its pharmaceutically acceptable salts



where, R is



the process comprising the steps of

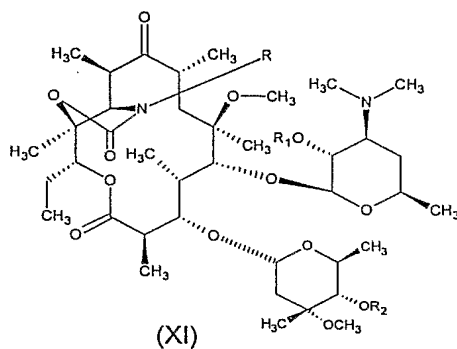
(a) reacting compound of formula (IX) with carbonyldiimidazole in presence of a polar solvent and base to obtain



(X)

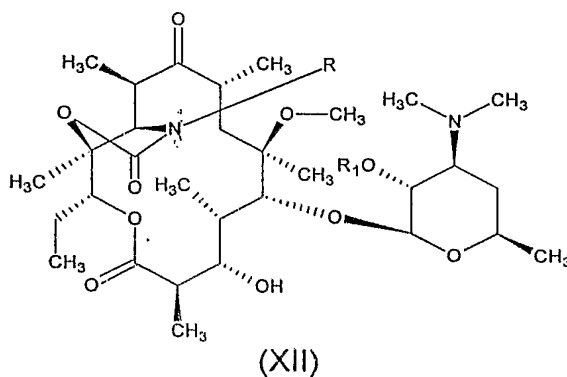
$$\text{R}_d - \text{C}(=\text{O}) -$$

(b) condensing the compounds of formula (X) with R-NH<sub>2</sub> in a suitable polar solvent to obtain compounds of formula (XI)

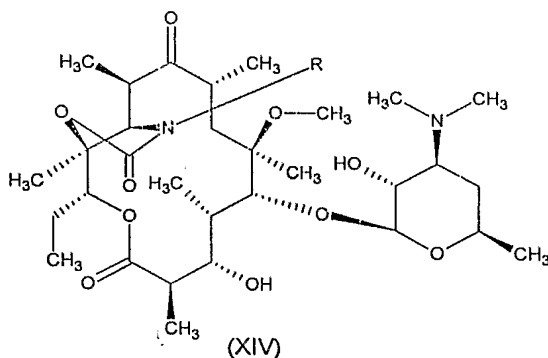


where R is as defined above and R<sub>1</sub> and R<sub>2</sub> are same or different protecting groups as described above;

- (c) treating the obtained compound formula (XI) with an acid to give compound of formula (XII)



- (d) treating compounds of formula (XII) with an alcohol to give compounds of formula (XIV)



- (e) oxidizing the resulting compounds of formula (XIV) of step (d) in presence of oxidizing agent to form desired ketolide compounds of formula (I).
3. The process as claimed in claim 2 wherein Telithromycin of formula (I) is prepared in a pure form by crystallizing the compound of formula (XIV) with a polar solvent.
  4. The process as claimed in claim 3 wherein the polar solvent is selected from alcohol or acetone and the polar solvent for crystallization is preferably acetone.
  5. A process as claimed in claim 1, wherein said polar solvent in step (a) is selected from dimethylformamide, tetrahydrofuran, acetonitrile and mixtures thereof.
  6. A process as claimed in claim 1, wherein said base in step (a) is selected from DBU, triethylamine, diisopropylethylamine.

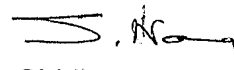
7. A process as claimed in claim 1, wherein said polar solvent in step (b) is selected from group comprising of methanol, ethanol, propanol, butanol, i-butyl alcohol, t-butyl alcohol, methoxyethanol, ethoxyethanol, pentanol, neo-pentyl alcohol, t-pentyl alcohol, cyclohexanol, ethylene glycol, propylene glycol, benzyl alcohol, phenol, glycerol, dimethylformamide (DMF), dimethylacetamide (DMAC), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMI), N-methylpyrrolidinone (NMP), formamide, N-methylacetamide, N-methylformamide, acetonitrile, dimethylsulfoxide, propionitrile, ethyl formate, methyl acetate, hexachloroacetone, HMPA, HMPT, acetone, ethyl methyl ketone, ethyl acetate, isopropyl acetate, t-butyl acetate, sulfolane, N,N-dimethylpropionamide, nitromethane, nitrobenzene, tetrahydrofuran (THF), dioxane, water, polyethers or mixtures thereof.
8. A process as claimed in claim 7, wherein said polar solvent is selected from dimethylformamide or acetonitrile.
9. A process as claimed in claim 1, wherein said step (b) is carried out at a temperature 5°C to 120° C.
10. A process as claimed in claim 9, wherein the said step (b) is carried out preferably at a temperature 30°C to 60° C.
11. A process as claimed in claim 1, wherein the said acid in step (c) is selected from organic or inorganic acid.
12. A process as claimed in claim 11, wherein the said acid is selected from the group comprising of hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid or hydrofluoric acid.
13. A process as claimed in claim 12, wherein the acid is preferably hydrochloric acid.
14. A process as claimed in claim 1, wherein step (c) is carried out in a solvent selected from water, polar organic solvents and mixtures thereof.
15. A process as claimed in claim 14, wherein said solvent is selected from water or alcohol or mixtures thereof.

16. A process as claimed in claim 15, wherein said solvent is selected from water, methanol, ethanol, isopropanol, n-propanol, tert-butanol, n-butanol or mixtures thereof.
17. A process as claimed in claim 1, wherein said step (c) is carried out at a temperature 0°C to 70° C
18. A process as claimed in claim 17, where in step (c) is carried out at a temperature 20°C to 60° C
19. A process as claimed in claim 1, wherein oxidation said in step (d) is carried out using Corey- Kim oxidation method, Des- Martins reagent, Pfitzner moffat method or modifications thereof or with dimethyl sulfoxide in presence of oxalyl chloride or phosphorous pentoxide or p-Toluene sulfonyl chloride or acetic anhydride or by manganese or chromium or selenium reagents, tert-amine oxides or any said oxidant in presence of phase transfer catalyst.
20. A process as claimed in claim 1, wherein alcohol said in step (e) is selected from group comprising of methanol, ethanol, n-propanol, iso propanol, tert-butanol, n-butanol or mixtures thereof.
21. A process as claimed in claim 20, wherein the said alcohol is preferably methanol.
22. A process as claimed in claim 1, wherein said step (e) is carried out at a temperature of 0°C to 100°C
23. A process as claimed in claim 22, wherein step (e) is carried out preferably at a temperature of 20°C to 70°C.
24. A process as claimed in claim 2, wherein said alcohol in step (d) is selected from group comprising of methanol, ethanol, n-propanol, iso propanol, tert-butanol, n-butanol or mixtures thereof.
25. A process as claimed in claim 24, wherein said alcohol is preferably methanol.
26. A process as claimed in claim 2, wherein said step (d) is carried out at a temperature of 0 to 70°C.
27. A process as claimed in claim 26, wherein the temperature is between 20 to 65°C.
28. A process as claimed in claim 2, wherein said oxidation in step (e) is carried out using Corey- Kim oxidation method, Des- Martins reagent, Pfitzner moffat method or

modifications thereof or with dimethyl sulfoxide in presence of oxalyl chloride or phosphorous pentoxide or p-Toluene sulfonyl chloride or acetic anhydride.

29. A process as claimed in claim 2, wherein oxidation in step (e) is carried out by manganese or chromium or selenium reagents, tert-amine oxides or any above oxidant in presence of phase transfer catalyst.

Dated this 23<sup>rd</sup> day of April 2004



Siddhartha Nag  
Of S. Majumdar & Co.  
Applicant's Agent